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To: Examiner Helene C. Bor

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From: J. Peter Paredes

Client/Matter: U.S. Application Serial No. 10/500,577, Confirmation No. 5236

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DOCUMENTS	NUMBER OF PAGES*
Draft Amendment and Response in light of Examiner's Interview for September 16, 2009 at 10am EST	13
TOTAL	14

Examiner Bor,

Please find the Draft Amendment for discussion during the Examiner's Interview scheduled for September 17, 2009 at 2pm EST.

Best regards,

J. Peter Paredes

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	J. Villard et al.	Attorney Docket:	6100-009
Serial No.:	10/500,577	Examiner:	Helene C. Bor
Filed:	12/27/2004	Art Unit:	3768
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Title: Methods and Compositions to Reduce Scattering of Light During Therapeutic and Diagnostic Imaging Procedures

Certificate of Facsimile Transmission

I certify that this document (along with any documents referenced as being included herewith) is being filed electronically on September 17, 2009 to: 571-273-2947.

Lori Dunham

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Commissioner for Patents
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DRAFT RESPONSE FOR EXAMINER'S INTERVIEW

Dear Sir:

This is a draft response for the Examiner's Interview to be conducted September 17, 2009 at 2pm EST as follows:

Claims:

1. (Previously Amended) A method for performing optical imaging or light-based treatment of at least a first tissue in an animal, comprising providing into the blood associated with said at least a first tissue a biologically effective amount of a low-scattering, oxygen-carrying blood substitute, wherein the low-scattering, oxygen-carrying blood substitute is selected to substantially reduce optical scattering from the blood fraction whilst substantially maintaining tissue oxygenation, and applying an optical imaging or light-based treatment step to said at least a first tissue.

2. (Original) The method of claim 1, wherein said low-scattering, oxygen-carrying blood substitute is a substantially non-particulate hemoglobin solution.

3. (Original) The method of claim 2, wherein said hemoglobin solution is a substantially non-particulate, homogeneous, acellular hemoglobin solution.

4. (Original) The method of claim 2, wherein said hemoglobin solution comprises bovine, porcine, ovine or primate hemoglobin.

5. (Original) The method of claim 2, wherein said hemoglobin solution comprises human hemoglobin.

6. (Original) The method of claim 2, wherein said hemoglobin solution comprises recombinantly produced hemoglobin.

7. (Original) The method of claim 2, wherein said hemoglobin solution comprises crosslinked hemoglobin.

8. (Original) The method of claim 2, wherein said hemoglobin solution comprises polymerized hemoglobin.

9. (Original) The method of claim 2, wherein said hemoglobin solution comprises glutaraldehyde crosslinked, polymerized hemoglobin.

10. (Original) The method of claim 2, wherein said hemoglobin solution comprises surface modified hemoglobin.

11. (Original) The method of claim 2, wherein said hemoglobin solution has a hemoglobin concentration of at least about 70% of the hemoglobin concentration of whole blood.

12. (Original) The method of claim 1, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the hematocrit of the blood associated with said at least a first tissue at least to about 10%.

13. (Original) The method of claim 12, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the hematocrit of the blood associated with said at least a first tissue at least to about 5%.

14. (Original) The method of claim 13, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the hematocrit of the blood associated with said at least a first tissue at least to about 4%.

15. (Original) The method of claim 14, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the hematocrit of the blood associated with said at least a first tissue at least to about 3%.

16. (Original) The method of claim 15, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the hematocrit of the blood associated with said at least a first tissue at least to about 2%.

17. (Original) The method of claim 16, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the hematocrit of the blood associated with said at least a first tissue at least to about 1%.

18. (Original) The method of claim 1, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the hematocrit of the blood associated with said at least a first tissue to between 0 and about 10%.

19. (Original) The method of claim 18, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the hematocrit of the blood associated with said at least a first tissue to between 1 and about 5%.

20. (Previously Amended) The method of claim 1, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the hematocrit of the blood associated with said at least a first tissue to an amount effective to result in a half maximal or lower scattering coefficient μ_s' according to the equation $\mu_{tot}' = \mu_a + \mu_s'$, where μ_a is the absorption coefficient and μ_{tot}' is the total attenuation coefficient.

21. (Original) The method of claim 1, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the hematocrit of the blood associated with said at least a first tissue to an amount effective to result in a scattering coefficient of about half the scattering coefficient for whole blood or less.

22. (Original) The method of claim 1, wherein said low-scattering, oxygen-carrying blood substitute is a solution comprising at least a first oxygen carrier, and wherein the largest species in said solution has a size of about 6 nanometers.

23. (Original) The method of claim 1, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the scattering coefficient of the blood associated with said at least a first tissue to about one half of the scattering coefficient of whole blood or less at a sample wavelength of between about 600 nm and about 1500 nm.

24. (Original) The method of claim 23, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the scattering coefficient of the blood associated with said at least a first tissue to about one tenth of the scattering coefficient of whole blood or less at a sample wavelength of between about 600 nm and about 1500 nm.

25. (Original) The method of claim 23, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the scattering coefficient of the blood associated with said at least a first tissue to about one half of the scattering coefficient of whole blood or less at a sample wavelength of about 600 nm.

26. (Original) The method of claim 25, wherein provision of said low-scattering, oxygen-carrying blood substitute reduces the scattering coefficient of the blood associated with said at least a first tissue to about one tenth of the scattering coefficient of whole blood or less at a sample wavelength of about 600 nm.

27. (Original) The method of claim 23, wherein provision of said low-scattering, oxygen-carrying blood substitute decreases the scattering coefficient of the blood associated with said at least a first tissue to a scattering coefficient of about 0.4 mm^{-1} or less at about 1310 nm.

28. (Original) The method of claim 27, wherein provision of said low-scattering, oxygen-carrying blood substitute decreases the scattering coefficient of the blood associated with said at least a first tissue to a scattering coefficient of about 0.3 mm^{-1} or less at about 1310 nm.

29. (Original) The method of claim 28, wherein provision of said low-scattering, oxygen-carrying blood substitute decreases the scattering coefficient of the blood associated with said at least a first tissue to a scattering coefficient of about 0.2 mm^{-1} at about 1310 nm.

30. (Original) The method of claim 1, wherein said low-scattering, oxygen-carrying blood substitute is a solution comprising at least a first oxygen carrier, and wherein the refractive index of said oxygen carrier is substantially equal to other molecular species in solution.

31. (Original) The method of claim 1, wherein said low-scattering, oxygen-carrying blood substitute has at least about 70% of the oxygen carrying capacity of whole blood.

Claims 32- 56 (Cancelled).

57. (Original) The method of claim 1, wherein said at least a first tissue is neural tissue.

58. (Original) The method of claim 1, wherein said at least a first tissue is brain tissue.

59. (Original) The method of claim 1, wherein said at least a first tissue is located within a highly perfused organ.

60. (Original) The method of claim 59, wherein said at least a first tissue is located within the kidney, lung, liver, spleen, brain, heart or one of the great vessels.

61. (Original) The method of claim 1, wherein said at least a first tissue is cardiovascular tissue.

62. (Original) The method of claim 1, wherein said at least a first tissue is cardiac tissue.

63. (Original) The method of claim 1, wherein said at least a first tissue is a blood vessel.

64. (Original) The method of claim 63, wherein said optical imaging or treatment step is applied from the lumen of said blood vessel.

65. (Original) The method of claim 63, wherein said blood vessel has or is suspected to have an atherosclerotic plaque or lesion.

66. (Original) The method of claim 1, wherein said at least a first tissue comprises at least two tissue layers, and wherein at least a first of said tissue layers is associated with a substantial blood fraction.

67. (Original) The method of claim 66, wherein said at least a first tissue comprises a plurality of tissue layers, and wherein at least a first of said tissue layers is associated with a substantial blood fraction.

68. (Original) The method of claim 1, wherein said animal has, or is at risk for developing, a cardiac tissue or cardiac valve defect.

69. (Original) The method of claim 1, wherein said animal has suffered, or is at risk for developing, a heart attack.

70. (Original) The method of claim 1, wherein said animal has, or is at risk for developing, an ischemic tissue.

71. (Original) The method of claim 1, wherein said animal has suffered, or is at risk for developing, a stroke.

72. (Original) The method of claim 1, wherein said animal has, or is at risk for developing, a vascularized tumor.

73. (Original) The method of claim 1, wherein said animal is a mouse.

74. (Original) The method of claim 1, wherein said animal is a human subject.

75. (Original) A method for optical coherence tomography imaging of a tissue in an animal, which tissue comprises a substantial blood fraction, comprising: (a) introducing into said blood fraction of said tissue an amount of an essentially non-particulate hemoglobin solution effective to substantially reduce optical scattering from said blood fraction whilst substantially maintaining oxygenation in said tissue; and (b) performing optical coherence tomography imaging of said tissue.

76. (Previously Amended) A kit comprising a low-scattering, oxygen-carrying blood substitute and instructions for using said blood substitute in an optical imaging or light-based treatment method, wherein the low-scattering, oxygen-carrying blood substitute is selected to substantially reduce optical scattering from a blood fraction whilst substantially maintaining tissue oxygenation.

77. (Original) The kit of claim 76, wherein said instructions are written instructions.

78. (Original) The kit of claim 76, wherein said instructions are computerized instructions.

79. (Original) A method for performing optical imaging or treatment of a tissue in an animal, which tissue comprises a substantial blood fraction, comprising: (a) introducing into said blood fraction of said tissue an amount of a low-scattering, oxygen-carrying blood substitute effective to substantially reduce optical scattering from said blood fraction whilst substantially maintaining oxygenation in said tissue; and (b) applying an optical imaging or treatment step to said tissue.

80. (Original) A method for performing optical imaging of at least a first tissue in an animal, comprising providing into the blood associated with said at least a first tissue a biologically effective amount of a low-scattering, oxygen-carrying blood substitute, and applying an optical imaging step to said at least a first tissue.

81. (Original) A method of generating an image of at least a first vascularized tissue by in vivo diagnostic light imaging, comprising providing into the blood perfusing said vascularized tissue a biologically effective amount of a low-scattering, oxygen-carrying blood substitute, and executing a diagnostic light imaging technique to generate an image of said vascularized tissue.

82. (Original) A method for optical coherence tomography imaging of at least a first tissue in an animal, comprising providing into the blood associated with said at least a first tissue a biologically effective amount of a substantially non-particulate hemoglobin solution, and performing optical coherence tomography imaging of said at least a first tissue.

Remarks

Claim Rejections - 35 USC § 102

I. Claims 1, 22, 63-71 & 79-81 rejected under 35 U.S.C. §102(b) as being anticipated by Loeb (U.S. Patent No. 4,448,188)

Claims 1, 79-81

The Examiner stated the following:

Loeb teaches a method for performing optical imaging [fiberoptic viewing system for sending a monochromatic light beam] (Col. 8, Line 47-54) or light based treatment [laser irradiation of the surface of the blood vessel for the removal of a plaque deposit] (Col. 3, Line 17-19) of at least a first tissue in an animal [blood vessel] (Abstract). Loeb teaches providing into the blood associated with first tissue a biologically effective amount of a low-scattering, oxygen-carrying blood substitute [substantially clear oxygen-bearing liquid] (Col. 4, Line 26-35). Loeb teaches wherein the low-scattering, oxygen-carrying blood substitute is selected to substantially reduce optical scattering [permit viewing with the blood vessel or use of the laser] (Col. 4, Line 22-25) from the blood fraction whilst substantially maintaining tissue oxygenation (Col. 3, Line 48-55). Loeb teaches applying an optical imaging or light-based treatment step to said at least a first tissue (Col. 3, Line 10-19).

The Applicant respectfully disagrees.

Loeb does not teach or suggest "a biologically effective amount of a low-scattering, oxygen-carrying blood substitute, wherein the low-scattering, oxygen-carrying blood substitute is selected to substantially reduce optical scattering", as to anticipate claim 1. The Examiner cites to the substantially clear oxygen-bearing liquid in Loeb, where substantially clear is to be understood that the transparency of the liquid or gas is sufficient to permit viewing within the blood vessel by use of a viewing system. Loeb, Col. 4, Lines 22-35, underlined added. In the field of optics, transparency is the physical property of allowing light to pass through a material, which allows much of the light that falls on the material to be transmitted, with little being reflected. However, scattering is a general physical process where light is forced to deviate from a straight trajectory by one or more localized non-uniformities in the medium through which light passes, and includes deviation of reflected radiation from the angle predicted by the law of reflection. As such, a material that is transparent may not necessarily be non-scattering.

Most importantly, Loeb teaches and enables that the oxygen-bearing liquid is a perfluorocarbon (PFC) emulsion. While PFC emulsions are transparent, PFC emulsions are not effective at reducing attenuation or reduce scattering, because the solution contains micron-scale particles that will scatter light similar to red blood cells. See Villard et al. thesis at 36-37, Villard

'2001, cited in IDS and in Office Action dated November 17, 2008. Moreover, the present application states that PFC's are unsuitable for use in the present invention because PFC's cause significant light scattering due to the size of PFC's being sufficiently close to the wavelengths of light used in imaging and light therapy (600-1500 nm). Present Application, Pages 23, line 30-Page 24, line 5. The inventors even validated that PFC's are unsuitable for use in the present invention due to their scattering properties. *Id.* As such, the substantially clear/ transparent oxygen-bearing liquid in Loeb does not teach or suggest a low-scattering, oxygen-carrying blood substitute, wherein the low-scattering, oxygen-carrying blood substitute is selected to substantially reduce optical scattering. Therefore, the rejection under §102(b) is improper and respectfully requested to be withdrawn.

II. Claims 2-21, 23-31, 57-62,72-74 & 76-78 rejected under 35 U.S.C. §103(a) as being unpatentable over Loeb (US Patent No. 4,448,188) as applied to claim 1 , 22,63- 71 & 79-81 above, and further in view of Rameshraja et al., Current aspects in pharmacology of modified hemoglobins, Advanced Drug Delivery Reviews, Volume 40, Issue 3, Blood Substitutes, 28 February 2000, Pages 185-198

The Examiner stated the following:

Loeb teaches the hemoglobin solution contained human hemoglobin (Col. 4, Line 54) and teaches using perfluorocarbons as a blood substitute, but fails to teach a blood substitute with modified hemoglobins (Col. 5, Line 13-33). However, Rameshraja teaches that two types of blood substitutes are in advance stages of development: perfluorocarbons (PFC) and modified hemoglobins. Rameshraja teaches PFCs have disadvantages such as inherent immunological response and higher risk to develop infection (Page 186, 1. Introduction) and many new developments regarding modified hemoglobin have been done to improve its physiological properties. Rameshraja teaches a blood substitute which comprises human hemoglobin (Page 193, Part 2.7). Rameshraja teaches a blood substitute which is substantially non-particulate, acellular, bovine hemoglobin solution [Oxyglobin] (Page 187, Part 2 & Page 192, Part 2.6) which allows for improved oxygen metabolism at the cellular level (Page 192, 2.6). It would have been obvious to one of ordinary skill in the art to substitute the blood substitute of Loeb with the Oxyglobin as taught by Rameshraja in order to have improved oxygen metabolism at the cellular level (Page 192, 2.6)

The Applicant respectfully disagrees.

Rameshraja states that "Biopure in 1998 received the clearance from Food and Drug Administration (FDA) to market the first ever 'blood substitute' Oxyglobin™ (HBOC-301, hemoglobin glutamer-200(bovine)) for the treatment of anemia in dogs. Rameshraja, Page 192, Part 2.6, Col. 1. HBOC-301 is not further mentioned or discussed in Rameshraja. Rameshraja states that HBOC-201 may allow for improved oxygen metabolism at the cellular level, and that

(HBOC-201) is a glutaraldehyde polymerized bovine hemoglobin. Rameshraja, Page 192, Part 2.6, Col. 1-Col. 2. Therefore, it would not have been obvious to one of ordinary skill in the art to substitute the blood substitute of Loeb with the Oxyglobin as taught by Rameshraja in order to have improved oxygen metabolism at the cellular level, because Rameshraja does not state that Oxyglobin improves oxygen metabolism at the cellular level.

Claims 23-30

The Examiner stated the following:

Loeb teaches the blood substitute to be substantially clear to allow for optical viewing or use of a laser. Also Loeb teaches a method for maximizing for the desired transparency to a particular laser wavelength (Col. 4, Line 43-46). Rameshraja teaches using a blood substitute [Oxyglobin@] with physical properties (Page 192, Part 2.6) that are inherent to the blood substitute as disclosed with the Applicant's Specification (Page 24-25).

The Applicant respectfully disagrees for the reasons stated below.

The Examiner stated that

While Applicant directs claims to certain observable properties when low-scattering, blood substitute is infused into the patient in the manner disclosed, the measured properties as claimed are inherent results. Applicant's description on page 29 gives evidence to the inherent properties.

The Examiner is inappropriately using Applicant's own invention to show that Oxyglobin includes inherent properties of "the low-scattering, oxygen carrying blood substitute is selected to substantially reduce optical scattering from the blood fraction whilst substantially maintaining tissue oxygenation". No where in the prior art references, Examiner's reasoning or rationale, is there shown or provided that Oxyglobin would have or result in the low-scattering, oxygen carrying blood substitute is selected to substantially reduce optical scattering from the blood fraction whilst substantially maintaining tissue oxygenation. The Examiner cites to Example 1 of the present application, where the inventors determined the effect of OCT signal attenuation at a wavelength of 1310nm due to blood in the murine Right Ventricle (RV), dilutions were placed between two glass slides separated by a 0.15 mm air space. The inventors selected a 0.15 mm distance as a compromise between obtaining sufficient signal amplitude from the lower surface at high hematocrit (e.g., 45%) and a measurable attenuation at low hematocrit (e.g., 5%). The inventors recorded OCT images through the sample dilutions prepared at the same hematocrits as above, i.e., 40, 30, 20, 10, 8, 5, and 3%. The results indicated to the inventors that the scattering properties of whole murine blood decreased from 1.801 +/- 0.245 to 0.253 +/- 0.176 1/mm ($p<0.05$) when the hematocrit was reduced from physiological levels to <5%. No where is it

shown in the prior art references or by the Examiner's rationale that Oxyglobin would include decreased scattering properties from 1.801 +/- 0.245 to 0.253 +/- 0.176 1/mm ($p<0.05$) when the hematocrit was reduced from physiological levels to <5% by placing dilutions of blood to hematocrits of 40, 30, 20, 10, 8, 5, and 3% between two glass slides separated by a 0.15 mm air space and detecting OCT signal attenuation at 1310 nm due to blood in the murine Right Ventricle (RV). Again, the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).

More so, Example 1 in the present application clearly shows that the "low-scattering, oxygen carrying blood substitute is selected to substantially reduce optical scattering from the blood fraction whilst substantially maintaining tissue oxygenation" is an unobvious difference in the prior art. The Examiner indicated that the burden is shifted to the applicants to prove that the subject matter to be shown in the prior art does not possess the characteristic relied on". *In re Fitzgerald*, 619 F.2d 70, 205 USPQ 596 (CCPA 1980). Using Oxyglobin to show decreased scattering properties from 1.801 +/- 0.245 to 0.253 +/- 0.176 1/mm ($p<0.05$) when the hematocrit was reduced from physiological levels to <5% by placing dilutions of blood to hematocrits of 40, 30, 20, 10, 8, 5, and 3% between two glass slides separated by a 0.15 mm air space and detecting OCT signal attenuation at 1310 nm due to blood in the murine Right Ventricle (RV) clearly shows that one of ordinary skill in the art would not use Oxyglobin in such manner, steps, or preparation to show a low-scattering, oxygen carrying blood substitute is selected to substantially reduce optical scattering from the blood fraction whilst substantially maintaining tissue oxygenation. As such, the steps of substantially reducing optical scattering from the blood fraction whilst substantially maintaining tissue oxygenation is an unobvious difference in the prior art and any rationale provided by the Examiner.

Finally, the Examiner is reminded that the pending claims are method or process claims and not claiming the product itself. The Examiner stated the following:

Products of identical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present.

Claim 1 claims the "method for performing optical imaging or light-based treatment of at least a first tissue…providing into the blood associated with at least a first tissue a biologically effective amount of a low-scattering, oxygen-carrying blood substitute, wherein the low-

scattering, oxygen-carrying blood substitute is selected to substantially reduce optical scattering from the blood fraction whilst substantially maintaining tissue oxygenation...".

III. Claims 75 & 82 rejected under 35 U .S.C. §103(a) as being unpatentable over Loeb (US Patent No. 4,448,188) as applied to claims 1 , 22, 63-71 & 79-81 above, and further in view of Swanson et al. (US Patent No. 5,321,501).

The Examiner stated the following:

Loeb teaches using a fiberoptic viewing system (Col. 8, Line 46-54) but fails to teach optical coherence tomography. However, Swanson teaches optical coherence tomography (Figure 1 B & Claim 2) for producing cross-sectional images (Col. 4, Line 59-63) with sharp focus and sensitivity (Col. 2, Line 24-33). It would have been obvious to one of ordinary skill in the art to modify the method of Loeb to include the optical coherence tomography imaging as taught by Swanson in order to produce cross-sectional images (Col. 4, Line 59-63) with sharp focus and sensitivity (Col. 2, Line 24-33).

The Applicant respectfully disagrees. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 409, 82 USPQ2d 1385, 1396 (2007). There is no showing or enablement that one of ordinary skill in the art would be able to modify the fiberoptic viewing system in Loeb with the OCT system as taught by Swanson. The fiberoptic viewing system includes means for supplying viewing light through the distal end 24 of the conduit 22, which can be accomplished by transmitting a light through the fiberoptic viewing bundle 28 or as shown in FIG. 2, by providing a separate light transmitting bundle 48; and the use of a separate light transmitting bundle is preferred for sending a monochromatic light beam through the fiberoptic viewing bundle 28. Loeb, Col. 8, lines 47-54. However, Swanson's Figure 1B teaches an optical frequency domain reflectometer utilizing a spectrally coherent optical source 79 which is frequency modulatable in the form of a linear FM chirp by signal generator 78; the output from source 79 passes to a sample assembly 28 and to a reference mirror 44; since changes in optical path length are not being utilized for this embodiment to perform longitudinal scanning, the remainder of the reference assembly shown in FIG. 1A is not required nor are modulators 34, 38 and 40; and a lens such as lens 36 may or may not be required. Such features and limitations of Swanson's OCT system render any combination with Loeb's fiberoptic viewing system questionable and inoperable.

Conclusion

According to the amendments and arguments presented above, the Applicant respectfully submits that the cited references fail to anticipate or render obvious the present invention and pending claims 1-31, 57-63, and 65-82 are in allowable form and allowance is respectfully requested.

Respectfully submitted

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September 17, 2009

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